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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/810,670	03/19/2001	Akiko Itai	P20797	9032

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EXAMINER
MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/810,670	ITAI ET AL.	
	Examiner	Art Unit	
	Marjorie A. Moran	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/16/05 has been entered. Claims 1-9 are pending.

All rejections and objections not reiterated below are hereby withdrawn in view of the amendment filed 12/16/05.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-9 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-9 are directed to methods for selecting lead-candidate compounds capable of binding as a ligand to a biopolymer. Claim 1 recites a single step of selecting a trial compound. Claims 2-9 recite further in silico steps. These steps are ones of mathematical manipulation; the claims do not recite a physical step or physical transformation of matter. Where a process claim does not recite a physical

transformation of matter, it MAY be statutory where it recites a practical application; i.e. a concrete, tangible and useful result.

Claim 1 now recites a step of "selecting" a compound. Claim 2 recites an "automatic" construction of a structure. Claims 5-7 recite in silico screening steps. None of these are physical steps or result in any transformation of matter for one form to another. While the result of a "selecting" of "screening" step may be concrete, the results are not communicated in a tangible form useful to one performing method, therefore the claims fails to recite a concrete, tangible and useful result. For a further discussion, applicant is referred to the "Patent eligible Subject Matter Guidelines" published at 1300 OG 142 (22 Nov. 2005).

Applicant's arguments filed 12/16/05 have been fully considered but they are not persuasive. The argument that the claims now recite "for the mode of covalent bond" as set forth on page 7 is confusing as this limitation is neither a physical step nor a concrete, tangible and useful result. Use of a "database" is not a physical step and therefore does not render the claim statutory; the "use" is merely one of comparing data. An "ability" to identify, compare, select, etc. candidates from a database is certainly interesting, but an "ability" or "capability" of performing a step is NOT a concrete or tangible RESULT. In response to the argument on page 8 of the response that the *specification* indicates that the claimed method produces a concrete, tangible and useful result, applicant is reminded that the CLAIMS must recite a concrete, tangible and useful result, and that limitations from the specification may not be "read into" the claims. Thus, the arguments are not convincing.

As the claims do not recite a physical transformation or a concrete, tangible and useful result for the reasons previously set forth and set forth above, the rejection is maintained.

Claims 1-9 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The claims are directed to methods for selecting lead-candidate compounds capable of binding "as a ligand" to a biopolymer but the claims fail to actually recite any step of selecting a lead-candidate compound or a ligand. Claim 1 recites a single step of selecting at least one trial molecule, but fail to recite any actual step of selecting a "lead compound" which is "capable of binding as a ligand" to a biopolymer, as claimed. As no "lead compound" or ligand is actually selected, the claims do not produce an "immediately useful" result.

Applicant does not address this rejection in the response filed 12/29/05, and the amendment does not overcome the rejection for the reasons set forth above, therefore the rejection is maintained.

Claim Rejections - 35 USC § 112, 1st para.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following includes both a lack of enablement and a lack of scope of enablement rejection.

The claims are not enabled for SELECTION of a lead-candidate compound which binds to any type of biopolymer because neither the specification nor the prior art teach specific parameters for selection of a compound or compounds which bind to any (generic) biopolymer.

Claims 1-9 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for identifying compounds capable of binding as ligands to proteins such as dihydrofolate reductase, does not reasonably provide enablement for identifying compounds which bind to any other type of biopolymer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Where the claims read on merely identifying compounds/ligands capable of binding to a biopolymer, the claims are enabled for identifying compounds which may bind to proteins such as dihydrofolate reductase because the specification teaches how to perform docking assays with proteins found in structural databases such as the Cambridge Crystallographic Database (CCD) or the Brookhaven Protein Data Bank

(PDB), but are not enabled for identifying compounds which bind to any other type of biopolymer because neither the specification nor the prior art teach how to do so.

The factors to be considered in determining what constitutes undue experimentation were affirmed by the court in *In re Wands* (8 USPQ2d 1400 (CAFC 1986)). These factors are the quantity of experimentation; the amount of direction or guidance presented in the specification; the presence or absence of working examples; the nature of the invention; the state of the prior art; the level of skill of those in the art; predictability or unpredictability of the art; and the breadth of the claims.

The claims are quite broad as they are directed to selection of a lead-candidate compound capable of "binding as a ligand" to any type of biopolymer. The specification teaches, in examples, how to determine/identify compounds likely to bind to a protein, specifically dihydrofolate reductase. The specification does not teach particular conditions which must be met to select a compound as a "lead-candidate"; i.e. to single out any particular compound as being a "better" ligand than the others, or which binds more tightly than another, etc. The state of the prior art is such that docking programs for "fitting" a ligand into a binding site of a protein are known. See e.g. DESJARLAIS et al. (IDS ref: J. Med. Chem. (1988) vol. 31, pp. 722-729). DESJARLAIS teaches specific steps for "scoring" the fit between a receptor and candidate compounds and teaches on page 724 that a user may "select the number of top scoring candidates" to be saved for further energy minimization steps. It is noted that the claimed methods do not recite any particular steps of scoring or ranking candidate compounds similar to those of DESJARLAIS, such that a selection may be made of the "top" or "lead" candidates. It is further noted that DESJARLAIS teaches fitting only to proteins wherein the crystallographic structure is known (pp. 726-727). The prior art of NISHIBATA (IDS

ref: Tetrahedron (1991) vol. 47, no. 43, pp. 8985-8990) teaches design of drug candidates based on the KNOWN structure of protein receptors using the LORE program. Again, NISHIBATA teaches use of a protein with known crystallographic coordinates (p. 8987) and does not teach design of candidate compounds which bind to any other type of biopolymer. In addition, NISHIBATA teaches specific parameters for selection of nine "lead-candidate" structures from among the 300 possible structures generated (pp. 8987-8989). Amended claim 1 now recites either selecting or matching (see below) "for the mode of covalent bond" but fails to disclose any specific parameters which would allow on of skill in the art to know WHAT about the selection/matching is based on the "mode of covalent bond". For example, are only specific types of covalent bonds to be considered? Are certain types of bonds excluded, included, or perhaps weighted? Claim 1 recites "matching" compounds, but fails to recite what degree, if any, of similarity is required for a "match" . Neither the instant claims nor the specification disclose which parameters are to be used to determine "matching".

The level of skill in the art of docking/fitting is acknowledged to be high. Despite this, it would require undue experimentation for one of skill in the art to identify any compound capable of binding to a biopolymer other than a protein because such a method is not taught by the instant specification of the prior art, as set forth above. Further, it would require guesswork by a skilled practitioner to determine how to *select* a "lead-candidate" capable of binding to a protein or any other type of biopolymer because neither the specification nor the prior art teach conditions or parameters for

selection which are universal to all biopolymers. Conditions for determining the "best" or "lead" compounds depend on which algorithm is used, what type of protein is chosen, and what type of activity one is looking for in a "lead" compound. As one of skill in the art would have to guess at the parameters involved in selection and/or "matching" to a query molecule, this would require undue experimentation.

For the reasons set forth above, the claims are not enabled for selection of lead-candidate compounds of any type, and are enabled only for identification of compounds/ligands capable of binding to proteins, but not to any other type of biopolymer.

Applicant's arguments filed 12/19/05 have been fully considered but they are not persuasive. Applicant argues on pages 9-10 of the response that matching is made "for the mode of the covalent bond." This amendment neither clarifies nor enables the claims for the reasons set forth above and in the rejections under 35 USC 112, 2nd paragraph. The examiner maintains that the claims fail to recite any step of actually selecting a lead compound, and that parameters for selecting a compound as a LEAD (i.e. one which is "better" or has more "desirable" properties than others) are not disclosed anywhere. Applicant further argues on pages 11-13 that one skilled in the art would know how to select a lead compound by matching a query molecule with compounds stored in a database, wherein the database contains information on atomic types and covalent bonds. It is admitted that one skilled in the art would know how to obtain or calculate atomic and binding information, and would know how to COMPARE information for a specific molecule to information from a database. However, the

examiner maintains that as the specification fails to teach one skilled in the art what parameters are required to determine how to "match" a query molecule to information in the database, particularly using "modes of covalent bonds," one skilled in the art must guess at such parameters; e.g. does a "match" require 100% congruence between molecules for atomic types and covalent bonds, less than 100% (if so, what percentage of congruence is required?), 100% over a portion of a molecule, are some covalent bonds weighted more than others in determining a match, etc? This constitutes undue experimentation, therefore the examiner maintains that the claims lack enablement.

With regard to the lack of scope of enablement, applicant argues that the claimed method is enabled for identifying compounds which may bind to biopolymers other than proteins such as dihydrofolate reductase because the specification exemplifies how to identify compounds which bind to dihydrofolate reductase. This is not persuasive. It has been admitted in several office actions that the specification provides examples for identifying ligands for dihydrofolate reductase, and the prior art teaches how to do so for other proteins. HOWEVER, it is again noted that the term "biopolymer", as defined by the specification , encompasses polysaccharides, lipid chains, peptide nucleic acids, and oligonucleotides. Neither the prior art nor the instant specification teaches how to select a lead compound/ligand, for example, from a database comprising bond and atomic information for polysaccharides or lipid chains. Applicant does not provide, anywhere, any evidence that the claimed method steps, can in fact, be used to identify compounds "capable of binding" IN ANY WAY, specifically as

ligands, to a polysaccharide or oligonucleotide. For these reasons, the examiner maintains that the claims are not enabled for their full scope.

Claim Rejections - 35 USC § 112, 2nd para.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a method for selecting a lead candidate compound, and recite functional limitations of the compound (i.e. capable of binding as a ligand), in the preamble. However, the claim steps do not recite selection of a lead candidate compound or a ligand, as recited in the preamble. The sole step of claim 1 recites selection of a "trial compound" by matching to a "query molecule." It is unclear whether the "trial compound" or the "query compound" (or neither) is intended to be the lead compound and/or ligand of the preamble. The claims appear to be missing an element or nexus between the preamble and actual steps, thus the claims are indefinite.

Claim 1 recites the phrase "for the mode of covalent bond" in the last line. It is unclear what is to be "for" the mode of covalent bond; i.e. selecting a trail compound or matching at least one query molecule. If the latter, then it is further unclear what is meant by "matching ... for the mode of covalent bond." It is unclear whether the covalent bond types (modes) of a trial and a query compound are to be matched, or

whether something else is to be matched which comprises or is affected by the "mode of covalent bond." For these reasons, the claims are indefinite.

Claims 3 and 4 limit the matching step of claim1 to comprise particular steps. Claim 1, as amended, appears to limit a matching step to be "for the mode of covalent bond." As claim 1 now apparently specifically limits the matching step, it is now unclear whether the "matching" limitations of claims 3-4 are intended to replace that of claim 1, or are intended to be supplemental to that of claim 1. If the latter, then the rejection may be overcome by replacing "is performed by" with --further comprises-- in line 2 of each of claims 3 and 4.

Claim Rejections - 35 USC § 102

Claims 1-2 and 6-9 are rejected under 35 U.S.C. 102(b) as being anticipated by DESJARLAIS et al. (IDS ref: PNAS (1990) vol. 87, pp. 6644-6648).

DESJARLAIS teaches a computer-implemented method of structure based drug design of inhibitors (ligands) of HIV-1 protease (biopolymer) wherein DESJARLAIS obtains 3D information for both the protease and drug candidates from a database and fits the drug candidates into a model of the inhibitor binding site of the protein (p. 6644 and Methods and Results). DESJARLAIS teaches use of interatomic distances and covalent bonding to judge stability and "goodness of fit" (p. 6645 and Figure 1) and matches atoms in the covalent bonds to those of the query molecule (p. 6645); i.e. uses "modes of covalent bonds" for matching, thus claims 1-2 and 6-9 are anticipated.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571) 272-0720. The examiner can normally be reached on Mon,Wed: 7-1:30; Tue,Thur: 7:30-6; Fri 7-3:30 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marjorie A. Moran
Primary Examiner
Art Unit 1631

Marjorie A. Moran
3/30/06